

REVIEW ARTICLE

The Oklahoma Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome Registry: the Swiss connection

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Abstract

Objectives: Thrombotic thrombocytopenic purpura (TTP) was initially described as an uncommon and usually fatal disorder. With effective treatment it is more frequently diagnosed, the clinical presentations are more diverse, and long-term sequelae are becoming recognized. **Methods:** Patient data are from The Oklahoma TTP-hemolytic uremic syndrome (HUS) Registry, an inception cohort of 348 consecutive patients with their first episode of clinically diagnosed TTP or HUS, 1989–2006. The Registry enrolls all patients in a defined region who are diagnosed with TTP or HUS and for whom plasma exchange treatment is requested. ADAMTS13 activity has been analyzed on 235 (93%) of 254 patients since 1995 at the University of Berne, Switzerland. Patients are described by clinical categories, related to their associated conditions and clinically apparent etiologies, and by the presence of severe ADAMTS13 deficiency. **Results and conclusions:** The clinical spectrum of syndromes described as TTP is variable with multiple etiologies. Advances in clinical and laboratory investigation have provided better understanding of the pathogenesis of these syndromes, their clinical evaluation and management, and their long-term outcomes. In addition to new information about TTP, these studies provide a model for translational research to define the complete community spectrum of uncommon disorders.

Key words thrombotic thrombocytopenic purpura; hemolytic uremic syndrome; ADAMTS13; Registry

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Thrombotic thrombocytopenic purpura (TTP) has a dramatic history beginning with the initial reports by Moschowitz in 1924 and 1925 (1, 2). The description of all 271 reported cases through 1964 defined its natural history (3). In this era before effective treatment, 90% of patients died, some rapidly, as the original case (1, 2), others developing multi-organ failure over months (3). A pentad of clinical features, present in 88–98% of patients in the 1966 review (Table 1), was described as the characteristic clinical presentation and appropriate diagnostic criteria: thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal failure, and fever (3). With the introduction of effective plasma therapy

after 1970, there was more urgency for diagnosis requiring less stringent diagnostic criteria, apparent in a review of subsequently reported cases, 1964–1980 (Table 1) (4). Mortality decreased to 54%; the frequency of neurologic abnormalities, renal failure, and fever also decreased (4). The randomized clinical trial documenting the effectiveness of plasma exchange treatment compared to plasma infusion, performed by the Canadian Apheresis Group 1982–1989, remains the definitive study on the management of TTP, decreasing mortality to 22% (Table 1) (5). The inclusion criteria for this clinical trial were only the presence of thrombocytopenia and microangiopathic hemolytic anemia without another apparent etiology; the

Table 1 The evolution of TTP from a fatal disorder with five diagnostic features to a treatable disorder with two diagnostic features

	1925–1964 (3) (%)	1964–1980 (4) (%)	1982–1989 (5) (%)
Thrombocytopenia	96	96	100
Hemolytic anemia	96	98	100
Neurologic abnormalities	92	84	63
Renal failure	88	76	59
Fever	98	59	26
Death	90	54	22

frequency of neurologic abnormalities, renal failure, and fever decreased even further. Therefore the previous pentad of clinical diagnostic features became obsolete and the current diagnostic criteria, only the presence of thrombocytopenia and microangiopathic hemolytic anemia without another apparent etiology, were established. Effective treatment resulted in a remarkable transformation of TTP, increasing the number of patients diagnosed with TTP nearly 10-fold (6) and revealing new issues for long-term survivors (7).

In 1955, Gasser *et al.* reported five children with a fatal disorder characterized by renal failure, thrombocytopenia and microangiopathic hemolytic anemia, described as hemolytic-uremic syndrome (HUS) (8). HUS, like TTP, was initially thought to be an uncommon and fatal illness until the clinical spectrum was dramatically increased with the emergence of Shiga toxin-producing *Escherichia coli* O157:H7 as a cause of HUS (9, 10). *Escherichia coli* O157:H7 infection causing hemorrhagic enterocolitis is most common in young children; approximately 15% of children progress to what is now described as typical, diarrhea-associated HUS (10). With only supportive care, 97% of children survive but 9% of survivors develop end-stage renal disease (11).

In 1998, two groups reported the remarkable association of severe deficiency of ADAMTS13 (*A* *d*isintegrin *and* *m*etalloprotease with *t*hrombospondin-1-like repeats) with TTP (12, 13). The pathogenetic role of ADAMTS13, a plasma enzyme responsible for post-secretion processing of von Willebrand factor (VWF), had been anticipated by Moake and colleagues 16 years earlier by the observation of unusually large multimers of VWF in the plasma of patients with chronic, relapsing TTP (14). Patients with acquired TTP had autoantibodies that inhibited ADAMTS13 function (12, 13); rare patients with congenital TTP had mutations in the ADAMTS13 gene resulting in deficiency (15). Furthermore, severe deficiency of ADAMTS13 activity appeared to distinguish patients with TTP from patients with HUS (12). The discovery of ADAMTS13 deficiency promised to provide more accurate diagnosis of TTP and more rational application of plasma exchange treatment (16).

Table 2 Methodology for the clinical and translational investigation of uncommon disorders, used by The Oklahoma TTP-HUS Registry (19)

Inception cohort of all consecutive patients from a defined geographic region
Standardized, prospective data collection
Quantitative, reproducible definitions for clinical features and outcomes
Systematic, complete follow-up
Correlation of clinical data with molecular mechanisms of disease

However these initial impressions of greater clarity soon yielded to more complexity. The distinction of TTP, often described as having predominant neurologic abnormalities, from HUS, often described as having predominant renal failure, became indistinct since many patients were observed with both neurologic and renal abnormalities, or neither abnormality. In addition, many patients with acquired disorders had the diagnostic clinical features of TTP (5, 7) without severe ADAMTS13 deficiency (17) and some patients with congenital absence of ADAMTS13 activity had no evidence of TTP (18).

New perspectives on TTP have been developed with application of the principles of clinical and translational investigation (Table 2) (19). The first step is the identification of an inception cohort of consecutive, unselected patients from a defined geographic region. This avoids the inevitable selection bias of reports that only describe patients who have classical clinical features. This principle is essential for the study of uncommon disorders, such as TTP and HUS, that do not have precise diagnostic criteria. The next three principles describe the methods of patient analysis. These data from a complete community experience are then generalizable to other populations. The final criterion describes correlative studies, applying new molecular knowledge to an appropriate patient sample. Data using these methods have provided our current understanding of TTP, that more accurately reflects its heterogeneity and more clearly guides evaluation and management.

In this review, we concisely describe the current concepts of the etiology, evaluation and management of TTP from the perspective of the Oklahoma-Swiss collaboration, with citations primarily from our experience.

Methods

Patient data: the Oklahoma TTP-HUS Registry

The Registry is possible for two reasons: (i) the Oklahoma Blood Institute is the sole provider of plasma exchange services for all hospitals in 58 of the 77 counties in the State of Oklahoma, a region with a population of 2 310 000, and (ii) plasma exchange treatment is the standard care in our region for adults with either TTP or

Table 3 Organization of The Oklahoma TTP-HUS Registry

The Oklahoma Blood Institute provides all plasma exchange procedures for 58 of Oklahoma's 77 counties, a region with a population of 2 310 000

Plasma exchange is the standard treatment for adult patients with TTP or HUS and for children with TTP or atypical HUS

Therefore the Registry is an inception cohort of patients in whom TTP or HUS was diagnosed and plasma exchange treatment was requested

348 consecutive patients with their first episode of clinically diagnosed TTP or HUS have been enrolled from 1989 through 2006

ADAMTS13 activity has been measured on 235 (93%) of 254 patients since 13 November 1995

Follow-up is complete on 346 of 348 patients

HUS and for children with TTP or atypical HUS (Table 3). Therefore the Registry is an inception cohort of all consecutive patients within this region in whom the diagnosis of TTP or HUS is established and a decision to initiate plasma exchange treatment is made (17, 20). Though some children with diarrhea-associated HUS and severe neurologic abnormalities are also treated with plasma exchange, most of these children are treated only with supportive care and therefore are not included in the Registry. Consistency of evaluation is provided by one of the authors (JNG) who has seen 283 (91%) of the 312 patients enrolled during their initial episodes since January 1995. Regular follow-up of Registry patients is an important priority, to be confident that long-term outcomes are accurately documented. Follow-up is currently complete on 346 of the 348 Registry patients. The Oklahoma TTP-HUS Registry is approved by the Institutional Review Boards of the University of Oklahoma Health Sciences Center and each participating hospital.

Patients are assigned in a hierarchical, sequential order to one of six categories related to associated conditions and potential etiologies that were clinically apparent during their initial episode (17): (i) following hematopoietic stem cell transplantation (HSCT), (ii) pregnant/postpartum, (iii) drug association, (iv) bloody diarrhea prodrome, (v) presence of an additional or alternative disorder which may have caused the presenting features, and (vi) idiopathic, if none of the criteria for the previous five clinical categories were fulfilled. Demographic, clinical, and laboratory data are collected prospectively in a Microsoft Access[®] database (17).

Laboratory data: the Swiss connection

Serum for ADAMTS13 assays has been collected immediately before the first plasma exchange procedure beginning 13 November 1995. Since that time samples have been obtained on 235 (93%) of 254 patients. Nine of the 19 patients without samples died before plasma exchange

treatment could be begun; in the others, samples were not obtained. ADAMTS13 activity measurements were performed as previously described (12, 21).

Nomenclature of the syndromes

Names matter. The names applied to these syndromes may influence management decisions. Since the standard of care for patients with TTP is plasma exchange (5), the description of a patient as having TTP suggests a requirement for plasma exchange treatment. Because children with typical diarrhea-associated HUS are not usually treated with plasma exchange (10, 11), a diagnosis of HUS may suggest withholding plasma exchange treatment and providing only supportive care. Therefore, as plasma exchange may be appropriate for most adults who fulfill the diagnostic criteria of TTP, TTP is an appropriate designation for adults. In this review we describe adult patients as having TTP, whether or not they have neurologic abnormalities or renal failure and whether or not they have severely deficient ADAMTS13 activity. There are exceptions. Adults following allogeneic HSCT are no longer routinely treated with plasma exchange when a diagnosis of TTP is considered; therefore the diagnostic term transplantation-associated thrombotic microangiopathy (22–24) is more appropriate and has replaced the term TTP in these patients. Adults who have a prodrome of bloody diarrhea associated with *E. coli* O157:H7 infection may be appropriately described by the comprehensive term, TTP-HUS, since they have demographic and clinical features of both adults with severe ADAMTS13 deficiency and children with typical diarrhea-associated HUS (25). Children with hemorrhagic colitis caused *E. coli* O157:H7 followed by acute renal failure with thrombocytopenia and microangiopathic hemolytic anemia are described as HUS. Children with renal failure but without a diarrhea prodrome are described as atypical HUS. Children without renal failure are described as TTP. In this review, we focus on syndromes described as TTP.

Results and interpretation

The Oklahoma TTP-HUS Registry

Patient accrual. During the first 18 yr of the Oklahoma TTP-HUS Registry, 1989–2006, 348 consecutive patients with their first episode of clinically diagnosed TTP or HUS were enrolled (Table 3). Our impression is that all patients have had acquired disorders; we have not recognized any patients with congenital TTP or HUS. Because enrollment only involves data collection and follow-up without additional procedures or change in management, all patients have consented to participate. Follow-up is

complete on 346 patients. Twenty additional patients have been enrolled during these 18 yr who were not clinically diagnosed with their first episode of TTP or HUS. Twelve patients were diagnosed by renal biopsy demonstrating thrombotic microangiopathy; these patients are distinct from clinically diagnosed patients; some did not have thrombocytopenia and microangiopathic hemolytic anemia. Eight patients had their initial episode of TTP outside the Registry region or before the Registry began and were initially seen for a relapsed episode; these patients are distinct from patients presenting with their initial episode because their diagnosis was immediately apparent and ADAMTS13 activity $\leq 15\%$ was present in the seven patients in whom it was measured. Restricting our analyses to patients with their first episode of clinically diagnosed TTP or HUS provides the best representation of the community experience from a clinician's perspective. These data allow us to define the incidence and demographic features, the relative frequency of different clinical categories, the frequency of severe ADAMTS13 deficiency, and the clinical outcomes.

Incidence. The annual incidence estimate for all patients with a clinical diagnosis of TTP, standardized to United States population data for age, race, and gender, is $11.29/10^6$ population (26). The standardized annual incidence estimate for patients with severe ADAMTS13 deficiency ($< 5\%$ activity) is $1.74/10^6$ population (26).

Annual frequency. The number of patients enrolled increased steadily during the first 7 yr of the Registry (Fig. 1). Since that time, the number of patients enrolled annually has been consistent, with a possible decline during recent years. The initial annual increase of patients is parallel to the experience in Canada (6) that accompanied the advent of plasma exchange treatment (5). The availability of effective treatment for TTP has resulted in greater urgency for diagnosis and therefore has required less stringent diagnostic criteria. The clear result of this evolution is the diagnostic dilemma presented by acutely ill patients who fulfill current diagnostic criteria: the diagnosis of TTP must be considered, but thrombocytopenia and microangiopathic hemolytic anemia are common among acutely ill patients. In these patients the decision for plasma exchange is balanced between the risks of withholding effective treatment in a patient with

possible TTP vs. the risks from the plasma exchange procedure. The decreasing number of patients in recent years may be the result of increased appreciation of the risks of plasma exchange treatment with more critical patient evaluation.

Risks of plasma exchange treatment. The risks of plasma exchange procedures are often underestimated. For example, a recent prospective study of 1727 plasma exchange procedures reported no deaths and few major complications (27). However our experience is different. Beginning in 1996, data have been collected on each plasma exchange procedure in every patient. Through the first 9 yr of this study, 1996–2005, 57 (28%) of 206 consecutive patients had 73 major complications (Table 4) (28–30). Five (2.4%) patients died as a result of plasma exchange complications: three from hemorrhage caused by central venous catheter insertion and two from sepsis related to the indwelling catheter. Two additional patients had cardiac arrests with pulseless

Table 4 Complications of plasma exchange treatment for TTP

Data prospectively collected on 206 consecutive patients with clinically diagnosed TTP or HUS, 1996–2005
57 patients (28%) had 73 major complications. Categories of major complications were:
Systemic infection (31 patients)
Catheter or venous thrombosis requiring placement of a new catheter and/or preventing plasma exchange (20 patients)
Hemorrhage and/or pneumothorax requiring transfusion and/or placement of a chest tube (eight patients)
Hypotension requiring treatment with pressors (seven patients)
Hypoxia requiring mechanical ventilation (five patients)
Anaphylaxis with cardiac arrest (one patient)
Serum sickness requiring corticosteroid treatment (one patient)
Five patients (2.4%) died as a result of major plasma exchange complications
Three patients died because of hemorrhage caused by central venous catheter insertion
Two patients died because of bacterial sepsis presumably originating from the central venous catheter
Two additional patients had non-fatal cardiac arrest with pulseless electrical activity
Pericardial hemorrhage with tamponade caused the central venous catheter guide wire
Anaphylactic reaction to plasma

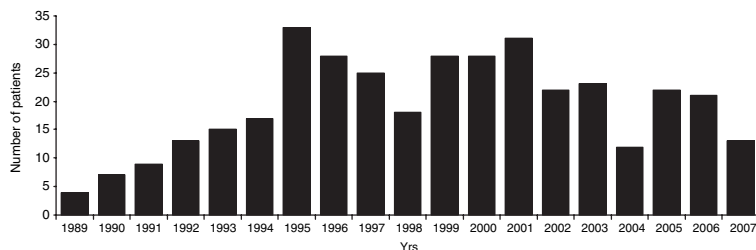


Figure 1 The number of patients enrolled in the Oklahoma TTP-HUS Registry each year, beginning 1 January 1989.

electrical activity and required extensive resuscitation; both recovered without sequelae. In one patient the arrest was caused by cardiac tamponade from gradual pericardial hemorrhage following perforation of the right ventricle by the internal jugular catheter insertion guide wire; the other patient had an anaphylactic reaction to plasma. The reason for our high rate of critical complications compared to other reports (27) may be related to the critical course of TTP compared to other disorders for which plasma exchange is used. Patients with TTP often require prolonged plasma exchange treatment, increasing the risk for catheter-related sepsis. Concomitant corticosteroid treatment for TTP may increase the risk for infection and also mask its symptoms. Other studies may not include patients who did not begin plasma exchange (27), thereby excluding patients with catheter insertion complications or death before treatment began. Our observations provide important reasons to restrict plasma exchange treatment to patients with a high probability of TTP.

Long-term outcomes. Effective treatment of TTP has not only resulted in long-term survival but has also revealed the presence of previously unrecognized problems. Although TTP has been considered to be a disorder with acute episodes and complete remissions, surviving patients often describe persistent difficulty with memory, concentration, and endurance (31). Neurocognitive tests suggest that patients may have residual abnormalities related to diffuse subcortical microvascular thromboses (32).

Clinical categories of TTP related to associated conditions and potential etiologies apparent during the initial episode

At the inception of the Oklahoma Registry, before knowledge of ADAMTS13 was available, we stratified patients according to clinical features of their initial episode (Table 5). These clinical categories were appropriate to define patients who may have different diagnostic and management issues and different outcomes. Each patient was only assigned to one clinical category, therefore a hierarchy of categories was established and patients were assigned in a sequential order. Even after the availability of ADAMTS13 measurements, these clinical categories have retained value for evaluation and management.

Hematopoietic stem cell transplantation. These critically ill patients commonly have thrombocytopenia and anemia with microangiopathic features due to multiple causes. The diagnosis of TTP is always uncertain. Patients in our Registry who have been diagnosed with TTP are significantly more likely to have major risks for complications, such as more severe underlying disease, multiple transplants, or an unrelated donor, and also to

Table 5 Clinical categories of 348 consecutive patients who presented with their first episode of clinically diagnosed TTP or HUS, 1989–2006

Stem cell transplant	23
Pregnant/postpartum	26
Drug-associated	44
Immune-mediated	26
Dose-dependent	18
Bloody diarrhea	24
Additional/alternative disorders	91
Idiopathic	140

have evidence for current complications, such as severe acute graft-vs.-host disease and sepsis (33). Because of the subjectivity of the diagnosis, there is also variability among physicians for considering the diagnosis of TTP. In the Registry, seven patients were diagnosed with TTP and treated with plasma exchange following HSCT in 1995, most by one physician contributing to the high total number of cases in this year (Fig. 1). All 23 patients who were diagnosed with TTP following HSCT have died; infection was confirmed as the cause of death in all of the six patients who had autopsies. Following these observations and also because of the absence of evidence for effectiveness of plasma exchange treatment, the rate of diagnosis among patients following HSCT diminished; no patients have been diagnosed with TTP following a HSCT since 30 March 2003. However analyses of all 20 autopsies following allogeneic HSCT at the University of Oklahoma, 1994–2005, supported the validity of the clinical diagnosis: the six who were diagnosed with TTP had extensive thrombotic microangiopathy in their kidneys; only two of the other 14 patients who were not clinically diagnosed with TTP had evidence of thrombotic microangiopathy ($P < 0.0001$) (34). The thrombotic microangiopathy limited to the kidneys was not consistent with the systemic thrombotic microangiopathy of TTP, and may have been result of toxicity from the preparative radiation/chemotherapy regimens or treatment with calcineurin inhibitors (34). Therefore these patients are now described as transplantation-associated thrombotic microangiopathy (22–24), rather than TTP, avoiding the implication that plasma exchange treatment may be appropriate.

Pregnancy/postpartum. Pregnancy is an important issue in TTP because most patients are women and most women are of child-bearing age. However evaluation of women who are pregnant or postpartum is often complicated by the occurrence of preeclampsia, eclampsia, and HELLP (*h*emolysis, *e*levated *l*iver function tests, *l*ow *p*latelets) syndrome. Although many of the 26 patients in our Registry associated with pregnancy may have had preeclampsia/eclampsia or HELLP syndrome, TTP was

a serious consideration because pregnancy is a potential trigger for acute episodes of TTP (18, 35). These observations have created concern about risks of future pregnancies in women who have survived episodes of TTP. A systematic review to identify all women reported with subsequent pregnancies identified 49 women with 70 subsequent pregnancies; recurrent TTP occurred in 41 (59%) pregnancies (36). However these reports may have been biased for describing adverse outcomes. Oklahoma Registry experience [previously published (36) plus subsequent patients] is half of the total published experience: 21 women have had 36 subsequent pregnancies; TTP was diagnosed in only five (14%) pregnancies. Two of these women had preeclampsia that could have caused the thrombocytopenia and microangiopathic changes, but because of concern for TTP withholding plasma exchange was not considered to be safe. Therefore the Registry experience suggests that recurrent TTP with subsequent pregnancies is uncommon. Based on these data, our practice has been to support women who wish to consider future pregnancies after discussion of the potential risks; frequent evaluations throughout pregnancy by their obstetrician and hematologist are essential.

Drug-associated TTP. Patients are described as having drug-associated TTP if they have taken a drug previously reported to be associated with TTP or HUS. This category is divided into two groups. One group appears to have immune-mediated disorders characterized by the abrupt onset of severe symptoms immediately following drug ingestion. The other group is characterized by the insidious onset of dose-dependent toxicity.

Quinine is the most common cause of immune-mediated drug-associated TTP, occurring in 23 of the 26 patients (Table 5) (37). The frequency of quinine-associated TTP is related to the ubiquitous use of quinine for over 60 yr for the very common symptom of nocturnal leg cramps (38, 39). The etiology of quinine-associated TTP is the presence of quinine-dependent antibodies that react with platelets and also multiple other cells and tissues (40, 41), causing a sudden severe systemic disorder, typically manifested by acute anuric renal failure. Because of the acute renal failure, patients with quinine-associated disease have also been described as HUS or TTP-HUS (37). The multiple systemic manifestations of quinine toxicity, such as liver function abnormalities and disseminated intravascular coagulation, often confuse the clinical presentation of TTP (42). Although prominent reports have described TTP associated with ticlopidine (43) and clopidogrel (44), these have been rare in our experience (three patients). Drug-dependent antibodies have not been reported in patients with suspected ticlopidine or clopidogrel associated TTP. Plasma exchange treatment seems appropriate for patients with quinine-

induced TTP because of the severity of disease and the frequent initial uncertainty about quinine ingestion in critically ill patients.

In contrast to the clinical course of quinine-associated TTP, thrombocytopenia, microangiopathic hemolysis, and renal failure following chemotherapeutic regimens or treatment with calcineurin inhibitors may be slowly progressive and may only become apparent after the presumed etiologic agent is discontinued. The diagnosis is often made by renal biopsy demonstrating thrombotic microangiopathy. The clinical course suggests an etiology of cumulative dose-dependent toxicity. Effectiveness of plasma exchange treatment is uncertain.

Bloody diarrhea prodrome. Twenty-four patients have presented with an acute bloody diarrhea prodrome, assumed to have an infectious etiology caused by *E. coli* O157:H7, similar to children with typical diarrhea-associated HUS. Therefore these patients may be appropriately described by the comprehensive term, TTP-HUS. The predominance of women (81%), frequent severe neurologic abnormalities (63%), and high mortality (31%) are distinct from children with diarrhea-associated HUS but the same as adults with severe ADAMTS13 deficiency (25). However the predominance of white race (95%), frequent acute renal failure (62%), and absence of relapses are distinct from adults with severe ADAMTS13 deficiency but the same as children with diarrhea-associated HUS (25). The severity and high mortality may reflect the greater risk for thrombotic complications in adults compared to the inherent resistance to thrombosis in young children. Plasma exchange seems appropriate because of the severity of disease and because patients with severe ADAMTS13 deficiency can present with bloody diarrhea caused by ischemic colitis (7, 25).

Additional disorders. Patients with a previous diagnosis of systemic lupus erythematosus (SLE) present difficult diagnostic problems because their systemic manifestations may be similar to TTP and each disorder can be mistaken for the other. Also SLE and TTP may coexist in the same patient, either simultaneously or sequentially (45). This overlap may be expected because TTP can also have an autoimmune etiology and both TTP and SLE are more frequent in young, black women (26, 45). Other additional disorders include other autoimmune diseases, such as scleroderma and polyarteritis nodosa, and HIV infection.

Alternative disorders. Many different systemic diseases can mimic all presenting features of TTP and be misdiagnosed with inappropriate initiation of plasma exchange treatment. When an alternative disorder was discovered, plasma exchange was stopped and appropriate treatment for the correct cause of the presenting clinical features was begun. Infections are the most common alternative diagnoses: fungal infections such as aspergillus, bacterial

infections such as endocarditis, viral infections such as cytomegalovirus, and rickettsial infections such as Rocky Mountain spotted fever have all been initially misdiagnosed as TTP (46). Many different malignancies can also mimic all clinical features of TTP and may not be recognized until a bone marrow biopsy is performed or until microscopic autopsy examination (47, 48). The lesson from this experience is to remain vigilant for alternative diagnoses even after an apparently firm diagnosis of TTP is established.

Idiopathic. Although many patients in the category of idiopathic TTP have severe ADAMTS13 deficiency, most patients do not (Table 6). The etiology of the presumed TTP in patients without severe ADAMTS13 deficiency is unclear. In some patients, other disorders, such as pancreatitis (49), appear to have provoked the acute episode of TTP.

Clinical importance of ADAMTS13 deficiency

Remarkably, only a minority of all patients in the Registry had severe ADAMTS13 deficiency (Table 6). The initial observations on ADAMTS13 deficiency in patients with TTP emphasized that a severe deficiency, often described as undetectable activity, is a specific abnormality for TTP (21). However, with more experience, the quantitative definition of a severe deficiency of ADAMTS13 has been adapted to be consistent with clinical observations. For example, using the more restrictive definition of less than 5% activity, all patients appear to have a clinical syndrome consistent with TTP; no patients were discovered to have an unexpected alternative diagnosis after plasma exchange treatment was begun that explained the presenting features and resulted in stopping plasma exchange treatments and beginning appropriate alternative treatment (Table 6). Yet this restrictive level excluded some patients who have all clinical features of TTP, including multiple relapses. A definition of less than 10% activity includes essentially all patients who are at risk for relapse (50) but also included two patients who were diagnosed with streptococcal

Table 6 Frequency of severe ADAMTS13 deficiency among 142 patients with a clinical diagnosis of TTP or HUS

Clinical category (number of patients)	ADAMTS13 activity	
	<5% Number of patients (%)	<10% Number of patients (%)
Stem cell transplant (7)	0	0
Pregnant/postpartum (10)	2 (20)	2 (20)
Drug-associated (21)	0	0
Bloody diarrhea (10)	0	1 (10)
Additional/alternative disorders (46)	0	2 (4)
Idiopathic (48)	16 (33)	20 (42)

Adapted from Ref. (17).

sepsis (one patient) and candida sepsis (one patient) immediately after the initial diagnosis of TTP; plasma exchange was stopped and appropriate antimicrobial treatment was begun. Higher levels of ADAMTS13 activity in some patients with TTP may merely be the result of multiple transfusions prior the diagnosis of TTP and measurement of ADAMTS13.

Role of ADAMTS13 measurements in patient evaluation. Table 7 documents the clinical features of patients with ADAMTS13 activity less than 5% (17). These patients are primarily young, overwhelmingly female, and half were black, consistent with the nine-fold greater relative incidence among blacks (26). These patients support the validity of current diagnostic criteria: half had no neurologic abnormalities at the time of their presentation, and most had normal serum creatinine values (Table 7) (17). The presenting symptoms of these patients were variable and non-specific; the most common symptoms were abdominal pain, nausea, vomiting, and diarrhea (17). Three patients had chest pain as their major symptom, consistent with cardiac ischemia (51, 52). Although TTP is characteristically considered to be an acute illness with abrupt onset, in four of these patients symptoms had been present for 2–3 wk (17).

Role of ADAMTS13 measurements in patient management. The outcomes of patients with severe ADAMTS13 deficiency were variable. Two patients died 3 and 17 d after diagnosis (17). One patient recovered completely with only five plasma exchange treatments and no adjunctive steroids or other immunosuppressive agents (Table 7). More often, patients required more than 3 wk of plasma exchange treatment, often required additional immunosuppressive therapy, and often had exacerbations of their illness requiring reinstitution of daily plasma exchange (17). Because prolonged and complicated clinical courses

Table 7 Demographic and clinical features of 18 consecutive patients with TTP and ADAMTS13 activity <5%

Age	36 (19–71) yr
Sex	14 (78%) female
Race	9 (50%) black
Neurologic abnormalities at presentation	
Severe	5 (28%)
Minor	4 (22%)
None	9 (50%)
Laboratory data	
Hematocrit	21 (15–30)%
Platelet count	11 (4–27) × 10 ⁹ /L
LDH	1640 (436–3909) U/L
Creatinine	1.2 (0.9–5.5) mg/dL
Deaths	2 (22%)
Number of plasma exchange treatments to achieve remission	23 (5–71)
Relapse (in survivors)	6/16 (38%)

are common, additional treatment is appropriate. We now routinely use corticosteroids in addition to plasma exchange in these patients; in some patients more intensive immunosuppression is required. Based on this experience, a clinical trial in the USA sponsored by the National Heart, Lung and Blood Institute will begin in 2008 to compare standard treatment (plasma exchange and corticosteroids) to standard treatment plus rituximab begun early in the course of treatment for patients with idiopathic or postpartum TTP, who may have ADAMTS13 deficiency (53). Although some patients do not require treatment other than plasma exchange (17), additional treatment with corticosteroids and possibly also rituximab may decrease the requirement for plasma exchange treatments and thereby diminish the risk for complications and may decrease the frequency of subsequent relapse.

Role of ADAMTS13 measurements for estimating long-term outcomes. The most important value of ADAMTS13 measurements is to recognize the risk for relapse (Table 7) (50). An important observation is that patients who do not present with severe ADAMTS13 deficiency very rarely relapse (50). However among patients with severe ADAMTS13 deficiency, those who relapse cannot be distinguished from those who do not relapse (50). Systematic serial evaluations of ADAMTS13 activity during remission have not been reported, although one case series suggests that persistence of severe ADAMTS13 deficiency may predict future relapse (54). However in our experience, with only occasional measurements during remission, it is apparent that some patients may have persistent severe deficiency for many years without clinical evidence for TTP.

Conclusions

TTP is a syndrome with multiple etiologies, diverse clinical presentations, and uncertain long-term outcomes. Clinical diagnostic criteria are limited and not precise, making the decision to initiate plasma exchange treatment difficult. Plasma exchange treatment for patients with TTP has a high rate of major complications and a mortality rate of 2.4%. Measurement of ADAMTS13 activity may not assist initial management decisions but does have important prognostic value. Patients with severe ADAMTS13 deficiency have a high risk for relapse while patients without severe ADAMTS13 deficiency rarely relapse. Although more than 80% of patients survive their acute episode, the frequency and significance long-term disabilities remain uncertain.

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